REMARKS

In response to the Office Action dated December 7, 2010, Applicants have canceled claims 3-4. The claim cancelations are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Claims 1-2 and 5-12 are pending and under examination. Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks.

CLAIM REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 3-4 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicants respectfully note that claims 3-4 have been canceled without acquiescence; thus, this basis of rejection is now moot and may be properly withdrawn.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103(A)

Claims 1-12 stand rejected under 35 U.S.C. § 103 (a), as allegedly being unpatentable over Hanenberg *et al.* or Rabbani *et al.* in view of Skorstengaard *et al.* (Eur. J. Biochem. 161, 441-453, 1986) and Kitazato *et al.* (U.S. Patent No. 7,226,786). Specifically, the Examiner alleges that the skilled artisan would have known how to use a polypeptide comprising the Fn1 domain, particularly fibronectin in a manner to increase gene transduction into a cell as evidenced by the teachings of Hanenberg *et al.* who disclose the use of compositions comprising fibronectin to increase the efficiency of retroviral gene transfer. The Examiner further alleges that Rabbani et al, also provide guidance for using fibronectin as a gene delivery substance. The Examiner concludes that one having skill in the art would have been motivated to substitute the complete sequence of bovine fibronectin disclosed by Skorstengaard *et al.* for the fibronectin disclosed by Hanenberg *et al.* or Rabbani *et al.* because it is *prima facie* obvious to substitute art recognized equivalents for the same purpose.

Applicants respectfully traverse this basis for rejection and submit that the Examiner has failed to provide a sufficient basis for one having ordinary skill in the art to predictably arrive at the presently claimed invention with any reasonable expectation of success. Thus, the Action fails to establish a *prima facie* case of obviousness against the presently claimed invention

It is the Examiner's burden to establish *prima facie* obviousness. *See In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993). Obviousness requires a suggestion of all the elements in a claim (*CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003)) and an explicit, apparent reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does with a reasonable expectation of success. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007).

Here, neither the cited references, nor the prior art suggest an actin acting substance comprising at least amino acids 21 to 241 of SEQ ID NO: 11, constituting an Fn1 domain, or a variant thereof for increasing the efficiency of introducing a target substance into a cell with any reasonable expectation of success.

Further, the Examiner has not provided any technical evidence or reasoning that would have prompted a person of ordinary skill in the relevant field to substitute the bovine fibronectin of Skorstengaard *et al.* for the fibronectin disclosed by Hanenberg *et al.* or Rabbani *et al.* for increasing the efficiency of introducing a target substance into a cell using an actin acting substance comprising an Fn1 domain as set forth in amino acids 21 to 241 of SEQ ID NO: 11 with any reasonable expectation of success. *See KSR v. Teleflex, Inc.* at 1741, citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.").

Applicants respectfully submit that Hanenberg *et al.* fail to suggest an actin acting substance comprising at least amino acids 21 to 241 of SEQ ID NO: 11 constituting an Fn1 domain, or a variant thereof. In contrast, Hanenberg *et al.* disclose recombinant fibronectin fragments consisting of fibronectin type III domains, *e.g.*, CH-271 and CH-296.

Applicants further submit that Rabbani *et al.* fail to suggest an actin acting substance comprising at least amino acids 21 to 241 of SEQ ID NO: 11 constituting an Fn1 domain, or a variant thereof. On the contrary, Rabbani et al. disclose that fibronectin binds retorviruses but does not bind to any other viruses, nucleic acids or nucleic acid constructs and thus, the use of fibronectin in this way is limited only to use with some retrovirus vectors and not with other virus vectors or with nucleic acids (*see, e.g,* paragraph [0006] of Rabbani *et al.*). In addition, Rabbani *et al.* only supports the covalent attachment of "fibronectin, a fibronectin fragment or fibronectin containing compounds … to either a polynucleotide or to a virus vector" (*see, e.g,* paragraph [0184] of Rabbani *et al.*) However, Rabbani *et al.* offer no guidance whatsoever to suggest any suitable fibronectins, fragments, or fibronectin containing compounds, let alone actin acting substance comprising at least amino acids 21 to 241 of SEQ ID NO: 11 constituting an Fn1 domain, or a variant thereof. Thus, the skilled artisan would have no reasonable expectation of success in selecting the claimed actin acting substances among the limitless number of fibronectins, fragments, or fibronectin containing compounds in existence. The Applicants' discovery of the significant effects of the claimed actin acting substance is detailed in paragraph [0347] of the instant specification. Applicants tested a number of fragments but the 29kDa domain, amino acids 21 to 241 of SEQ ID NO: 11, resulted in unexpected and surprising increases in transfection, *see, e.g.,* Figure 4.

Moreover, Skorstengaard *et al.* merely discloses the primary sequence of bovine fibronectin and domain structure of bovine fibronectin, but are completely silent with regard to an actin acting substance comprising at least amino acids 21 to 241 of SEQ ID NO: 11 constituting an Fn1 domain that can be used for increasing the efficiency of introducing a target substance into a cell.

Accordingly, and contrary the Examiner's conclusory reasoning, the skilled artisan would not have been motivated to substitute the complete sequence of bovine fibronectin disclosed by Skorstengaard *et al.* for the CH-271 and CH-296 fibronectin fragments disclosed by Hanenberg *et al.* or the limitless genus of fibronectins, fibronectin fragments or fibronectin containing compounds disclosed by Rabbani *et al.* to arrive at the presently claimed invention because full-length bovine fibronectin is not recognized in the art as being suitable for for

increasing the efficiency of introducing a target substance into a cell. *In Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492. F.3d 1350 (Fed. Cir. 2007), the Court noted that "In addition to structural similarity between the compounds, a *prima facie* case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure. *In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. 1985)." In addition, the Court clarified, that in order to find a *prima facie* case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. *Id.* (*citing In re Jones*, 958 F.2d 347 (Fed. Cir. 1992); *Dillon*, 919 F.2d 688; *Grabiak*, 769 F.2d 729; *In re Lalu*, 747 F.2d 703 (Fed. Cir. 1984)). Here, the Examiner has failed to articulate any prior art suggestion to modify the full-length bovine fibronectin to derive an actin acting substance comprising at least amino acids 21 to 241 of SEQ ID NO: 11, constituting an Fn1 domain, or a variant thereof for increasing the efficiency of introducing a target substance into a cell.

In addition, the Examiner alleges complete sequence of bovine fibronectin disclosed by Skorstengaard *et al.* for the fibronectin disclosed by Hanenberg *et al.* or Rabbani *et al.* because it is *prima facie* obvious to substitute art recognized equivalents for the same purpose. Applicants disagree and submit that the Examiner has only made conclusory allegations and has not provided any facts to support this basis of rejection.

Applicants submit that the Office has recognized that "[s]imply stating the principle (*e.g.,* "art recognized equivalent," "structural similarity") without providing an explanation of its applicability to the facts of the case at hand is generally not sufficient to establish a *prima facie* case of obviousness (*Federal Register*, Vol. 75, No 169, Sept. 1, 2010, page 53645). In addition, Applicants submit that the Office has determined that to reject a claim based on art recognized equivalency the Office personnel must resolve the Graham factual inquiries **and** must then articulate the following: (1) a finding that the prior art contained a device (method, product, etc.) which differed from the claimed device by the substitution of some components (step, element, etc.) with the other components; (2) a finding that the substituted components and their functions were known in the art; (3) a finding that one of ordinary skill in the art could have substitute one known element for another, and the results of

the substitution would have been predictable; and (4) whatever additional findings based on the Graham factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness. Here, at the very least, the Examiner has not articulated any fact-based reasoning to support that the full-length bovine fibronectin disclosed by Skorstengaard *et al.* and the fibronectin disclosed by Hanenberg *et al.* or Rabbani *et al.* have equivalent functions that were known in the art and thus, no basis to support why the results of the substitution would have predictable.

In addition, Applicants respectfully submit that Kitazato *et al.* does not remedy the insufficiencies of Hanenberg *et al.*, Rabbani *et al.*, and Skorstengaard, and thus, all four references cited by the Examiner individually and collectively fail to establish a *prima facie* case of obviousness against the presently claimed invention.

Accordingly, for at least these reasons, Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case against the presently claimed one-pot synthesis.

Reconsideration and withdrawal of this basis for rejection is respectfully requested.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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